REMARKS

Claims 1-20 were pending in this application. Claims 12-20 are canceled herein without prejudice to pursuing these claims in a divisional application. Claims 1-11 have been amended. Claims 21-25 are new. The claims have been amended to more particularly and distinctly claim that which the Applicants regard as their invention.

In particular, Claim 1 is amended to recite a method of detecting or quantifying EGFRvIII in a mammal, comprising (a) obtaining a biological sample from the mammal; (b) obtaining an EGFRvIII-specific polyclonal antibody that does not cross react with EGFR; (c) performing an immunological test on the sample using the EGFRvIII-specific polyclonal antibody; and (d) detecting or quantifying EGFRvIII in the mammal. Support for this amendment can be found, *inter alia*, on page 4, lines 11-13, and on Figure 1 of the specification. Support for polyclonal antibody can be found inter alia on page 7, lines 12-14 and pages 5-6 of the specification, which describes production of polyclonal antibodies in mammals and subsequent purification of this polyclonal antibody by passing through an affinity matrix column containing EGFRvIII peptide.

Claim 2 is amended to become independent and to correct formal linguistic errors therein.

Claim 3 is amended to correct formal linguistic errors therein.

Claim 4 is amended to become independent and to correct formal linguistic errors therein.

Claim 5 is amended to correct formal linguistic errors therein.

Claim 6 is amended to recite a method of screening patients with cancer for anticancer therapy using the EGFRvIII-specific polyclonal antibody of the invention. Support for this amendment can be found, *inter alia*, in original claim 6 and page 10 of the specification.

Claim 7 is amended to become independent and to correct formal linguistic errors therein.

Claim 8 is amended to correct formal linguistic errors therein.

Claim 9 is amended to recite a method of detecting a preneoplastic disorder in a mammal using the EGFRvIII-specific polyclonal antibody of the invention. Support for this amendment can be found, *inter alia*, in original Claim 9, and pages 5-6 of the specification.

Claim 10 is amended to become independent and to correct formal linguistic errors therein.

Claim 11 is amended to recite that the benign prostatic hyperplasia is detected using the EGFRvIII-specific polyclonal antibody of the invention. Support for this amendment can be found, *inter alia*, in the original claims.

New Claim 21 is dependant on Claim 6 and recites that the cancer comprises breast cancer, adenocarcinoma, squamous lung cancer, gastrointestinal cancer, renal cell cancer, bladder cancer, glioma, gynecological carcinoma, or prostate cancer. Support for this claim can be found, *inter alia*, in the original claims.

New Claim 22 is dependant on Claim 6 and recites that the anticancer therapy comprises a vaccine, an antibody-toxin conjugate, an EGFRvIII-specific tyrosine kinase inhibitor, or a combination thereof. Support for this claim can be found, *inter alia*, in the original claim 6 and on page 3, lines 24-27 of the specification.

New Claim 23 recites a method of diagnosing cancer in a mammal using the EGFRvIII-specific polyclonal antibody of the invention. Support for this claim can be found, *inter alia*, on page 4 of the specification.

New Claim 24 is dependent on Claim 23 and recites that the EGFRvIII-specific polyclonal antibody has been rendered specific for EGFRvIII by absorption with one or more fragments of EGFR. New Claim 25 is dependent on Claim 24 and recites that the one or more fragments of EGFR comprise a peptide represented by SEQ ID NO: 2, a peptide represented by SEQ ID NO: 3, or both. Support for this claim can be found, *inter alia*, on pages 6-7 of the specification.

A paragraph has been inserted at page 6 to characterize the peptides listed in the Sequence Listing. It is apparent that SEQ ID NOS:1, 5 and 6, which span the deletion junction of EGFRvIII (LEEKKG-NYVVTDH), contain EGFRvIII epitopes, and that SEQ ID NOS:2, 3 and 7-9, which do not span the junction, contain EGFR epitopes.

The amendments to the claims and the specification do not constitute new matter as defined in 35 U. S. C. § 132. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

I. FORMAL MATTERS

A) Information Disclosure Statement

Applicants have filed an Information Disclosure Statement (IDS) on June 16, 2003 in the USPTO. The Examiner has not acknowledged the receipt of the Applicants' IDS. Applicants request the Examiner to acknowledge and consider Applicants' IDS by returning to Applicants the initialed copy of the PTO-Form 1449 dated June 16, 2003.

B) Restriction Requirement

The Examiner acknowledges Applicants' election of the invention of Group 1 directed to Claims 1-11. Applicants have cancelled Claims 12-20 directed to the non-elected invention of Group 2, without prejudice to pursuing these claims in a divisional application.

C) Indication of Allowable Subject Matter

The Examiner has indicated that Claims 2, 4, 7, 8, and 10 would be allowable if rewritten to overcome Examiner's rejections under 35 U. S. C. § 112, second paragraph. The Examiner's reasons for allowance of these claims, as indicated in the Office Action, are that no prior art teaches or suggests cancer diagnosis by using an ELISA assay to detect EGFRvIII from a mammal in biological samples, including urine, plasma, serum, amniotic fluid, breast secretions, lung sputum or tumor cell extracts. The Examiner states that the closest prior art is Wikstrand *et al.*, which is only capable of using biopsy tissue samples and not the samples recited in the claims, which samples are more practical and more convenient for clinical applications.

IV. REJECTION OF CLAIMS UNDER 35 U. S. C. § 112, SECOND PARAGRAPH

The Examiner rejects Claims 1-11 under 35 U. S. C. § 112, second paragraph as allegedly being vague and indefinite. Specifically, the Examiner rejects Claim 1 as reciting the abbreviation "EGFRvIII". Applicants respectfully submit that the full name of EGFRvIII is

recited in the specification on page 1, as "epidermal growth factor receptor vIII", upon its first occurrence. Accordingly, the abbreviation "EGFRvIII" in Claim 1 is not indefinite.

Also, with respect to Claim 1, the Examiner requires Applicants to spell out the word "ELISA". Applicants have amended the specification to recite the full name of ELISA "enzyme-linked immunosorbent assay", upon its first occurrence. Withdrawal of this rejection respectfully requested.

With respect to Claim 2, the Examiner requires Applicants to spell out "CSF" Applicants have amended the specification to recite the full name of CSF as "cerebrospinal fluid", upon its first occurrence. Withdrawal of this rejection is respectfully requested.

With respect to Claim 6, the Examiner objects to a typographical error in the word "ELISA". Applicants have amended Claim 6 to correct the word "ELISA". Withdrawal of this rejection is respectfully requested.

Also with respect to Claim 6, the Examiner states that it is unclear to one of ordinary skill in the art as to how to select a mammal for anticancer therapies and the relationship between the quantifying EGFRvIII from the mammals having cancer and the EGF-directed anticancer therapies. Applicants have amended Claim 6 to more clearly and distinctly claim the method of anticancer therapy of the invention. Withdrawal of this rejection is respectfully requested.

V. REJECTION OF CLAIMS UNDER 35 U. S. C. § 103

A) Rejection of Claims 1, 3, 5, 9, and 11 over Wikstrand *et al.*, in view of Morgan *et al.*

The Examiner rejects Claims 1, 3, 5, 9, and 11 under 35 U.S.C. § 103(a) as allegedly being obvious over Wikstrand *et al.* Cancer Res. 1997, 57: 4130-4140, (hereinafter "Wikstrand *et al.*") in view of Morgan *et al.* Specifically, the Examiner contends that Wikstrand *et al.* teaches assessing the qualitative distribution and quantitative expression of the EGFRvIII from neoplastic tissues by the use of the EGFRvIII specific monoclonal antibody L8A4.

While the Examiner notes that Wikstrand *et al.* does not disclose the use of ELISA for measuring the amount of EGFRvIII in the sample, it is the Examiner's position that Morgan *et al.* cures this deficiency by disclosing the use of ELISA as a common practice in the art once the specific monoclonal antibody is available. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the assay of Wikstrand *et al.* with the ELISA assay as taught by Morgan *et al.* to arrive at the claimed invention. Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that a rejection under 35 U. S. C. § 103 requires the Examiner to show that the references properly combined teach each and every element of the claimed invention. Applicants submit that the combination of the cited references, even if properly made, which is not admitted, fail to teach the subject matter of the rejected claims. Claim 1 is directed to a method of detecting and quantifying EGFRvIII by an ELISA that utilizes an EGFRvIII-specific polyclonal antibody. The antibody is rendered specific for EGFRvIII by absorption with fragments of wild-type EGFR. Wikstrand *et al.* does not teach an EGFRvIII-specific polyclonal antibody of the invention, nor does it teach the use of the ELISA assay of the invention as claimed. Wikstrand *et al.* discloses only an EGFRvIII monoclonal antibody, namely "mAb L8A4". There is no suggestion or teaching in Wikstrand *et al.*, for the use of a polyclonal antibody, which has been made specific for EGFRvIII, such as by removing antibodies that cross react with the wild type EGFR.

Morgan *et al.* does not cure the deficiencies of Wikstrand *et al.* with respect to the claimed invention. Morgan *et al.*, as noted by the by the Examiner, discloses the use of ELISA as an immunological test. While the use of ELISA for an immunological test is known in the art, the use of the novel EGFRvIII-specific polyclonal antibody of the invention in ELISA can not be obvious to one of ordinary skill in the art prior to the discovery of this antibody by Applicants. One of ordinary skill in the art following the teachings of Wikstrand *et al.* and Morgan *et al.* at best would be motivated to use mAb L8A4 in an ELISA test to detect immunoreactivity of mAB L8A4 against EFGRv peptides. Such an ELISA is not the subject matter of the rejected claims.

Accordingly, Claims 1, 3, 5, 9 and 11 are not *prima facie* obvious over the combination of the references.

Withdrawal and reconsideration of this rejection is respectfully requested.

B) Rejection over Moscatello *et al.* in view of Morgan *et al.*

The Examiner rejects Claim 6 as being obvious over Moscatello *et al.*, Cancer Res. 1997 57: 1419-1424, (hereinafter, "Moscatello *et al.*") in view of Morgan *et al.* Specifically, the Examiner contends that Moscatello *et al.* discloses that an EGFRvIII-derived polypeptide from the junction of EGFRvIII could serve as a basis for antitumor vaccine.

While the Examiner notes that Moscatello *et al.* does not disclose the use of ELISA for measuring the amount of EGFRvIII in the sample, it is the Examiner's position that Morgan *et al.* cures this deficiency by disclosing the use of ELISA as a common practice in the art. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the vaccine therapy of Moscatello *et al.* with the ELISA assay as taught by Morgan *et al.* to arrive at the claimed invention. Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants submit that to the extent that the Examiner's rejection is directed to the use of a vaccine as an anticancer therapy, Claim 6 as amended is no longer directed to the use of vaccines *per se* as an anticancer therapy.

Applicants respectfully submit that the combination of the cited references, even if properly made, which is not admitted, fails to teach the subject matter of Claims 6, and 22. Claim 6 is directed to a method of screening patients with cancer to receive anticancer therapy, wherein an ELISA uses an EGFRvIII-specific polyclonal antibody that does not cross react with EGFR. According to claim 22, the anticancer therapy selected for the patient comprises administration of a vaccine, an antibody-toxin conjugate, an EGFRvIII-specific tyrosine kinase inhibitor, or a combination thereof.

Moscatello *et al.* or Morgan *et al.*, either alone or in combination, does not teach or suggest the screening method of the invention as claimed. Moscatello *et al.* as noted by the Examiner, discloses the use of EGFRvIII peptide as an antitumor vaccine. Moscatello *et al.* does not teach or suggest the screening method anticancer therapy of the invention as claimed because

this reference does not disclose the EGFRvIII-specific polyclonal antibody or the use of this antibody in an ELISA to screen for the presence of EGFRvIII in the sample of patients as part of the screening method.

Accordingly, Claims 6, and 22 are not *prima facie* obvious over the combination of the references.

Withdrawal and reconsideration of this rejection is respectfully requested.

CONCLUSION

In light of the above, Applicant respectfully submits that all pending claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action dated November 18, 2003 (Paper No. 9).

The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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